REMARKS

Applicants respectfully request reconsideration of the present application in view of the foregoing amendments and the following commentary.

I. Status of the Claims

Claims 1-13, 16 and 22 were cancelled previously. Claims 14 and 24 have been amended to rephrase the claimed subject matter more clearly. Claim 25 has been added with support in the original specification, for example, at page 9, first full paragraph. Because no new matter is introduced, Applicants respectfully request entry of this amendment. Upon entry, claims 14-15, 17-21, and 23-25 will be pending, with claims 19-21 withdrawn.

II. Claim Objection

The Examiner objected to claim 24 for informalities. Claim 24 has been amended to recited the correct plural form, thereby obviating the stated basis for the objection.

III. Rejection of Claims under 35 U.S.C. § 102(b)

A. Ueno

The Examiner rejected claims 14, 17, 18, 23 and 24 for alleged anticipation by Ueno *et al.*, Nihon Yakugakkai Dai 121 nenkai Yoshishu, page 9, March 5, 2001, abstract for a meeting of the Pharmaceutical Society of Japan. Applicants respectfully traverse the rejection

The Examiner is heard to say that to the broadest interpretation, ERGIC-53 cargo receptor is a "modified" receptor that is VIP36, and *vice versa*. See Office Action, the first full paragraph at page 5 and page 10, respectively.

Claim 14 has been amended accordingly to explicitly recite the mutants of the cargo receptors ERGIC-53 and VIP-36, relative to their native counterparts, thereby obviating the stated rationale for the rejection.

Moreover, Ueno describes an MDCK cell capable of expressing a chimeric ERGIC-53 protein, in which the lectin domain is completely replaced by the lectin domain of BPA or MAH. In fact, BPA or MAH lectin is approximately 260 amino acids in size, whose entire region was employed for the replacement of ERGIC-53 lectin domain. By contrast, the claimed ERGIC-53 mutant comprises an alteration of at least one amino acid, relative to the native cargo receptor, in the sequence of the native cargo receptor's carbohydrate recognition domain, ***between amino acid residues 152 and 160,*** exclusive of the conserved residues at positions 152 and 156.

Importantly, as submitted in the response filed June 27, 2007, the chimeric ERGIC-53 protein disclosed by Ueno does not retain the function of being capable of transporting glycoproteins selectively in eukaryotic cells. This is so because the chimeric proteins remain localized in Golgi and cannot be mobilized into the cytoplasm.

ERGIC-53 and VIP-36 are animal lectins, which function within animal cells to effect glycoprotein sorting and quality control. See specification at page 6, lines 12-13. On the other hand, the cited art relates to BPA and MAH lectins, which are leguminous (plant) lectins. As a class, plant lectins protect the plant itself. A plant lectin, once bound to a virus or to a bacterium, does not release from it. By contrast, an animal lectin can capture and then release a ligand, via an "on/off" mechanism controlled by infra-Golgi pH or Ca^{2+} concentration. Thus, alterations to a cargo receptor of the invention allow the modified receptors to retain the glycoprotein-transporting function. Conversely, this important aspect of the invention is obviated when, pursuant to the examiner's rationale for rejection, one replaced the animal lectin with a plant lectin, eliminating the transporting function.

Noting, correctly, that the Golgi apparatus is a cellular organelle, the Examiner has questioned Applicants' previous response concerning whether the cargo receptor is able to be "mobilized into the cell" (Action, page 7, last paragraph). Applicants clarify that the chimeric ERGIC-53 protein of the Ueno reference remains localized in Golgi but cannot be mobilized into the cytoplasm.

The Examiner further contends that "applicants are arguing the intended use of the claimed product" by the claim recitation of a cargo receptor "[that] is capable of selectively transporting the glycoprotein in said cell"(Action, page 8, first paragraph). Applicants respectfully disagree.

Claim 14 recites a eukaryotic cell comprising heterologous DNA coding for a mutant of the native cargo receptor ERGIC-53, wherein the mutant is capable of selectively transporting the glycoprotein in said cell. In other words, the claimed eukaryotic cell comprises a mutant prescribed by a functional limitation, *i.e.,* "capable of selectively transporting the glycoprotein," which is enabled by the structural features, *i.e.,* the mutant "comprises an alteration of at least one amino acid…in the sequence of the native cargo receptor's carbohydrate recognition domain, between amino acid residues 152 and 160 of SEQ ID NO: 2."

As explained in the foregoing paragraphs, the structural features of the ERGIC-53 mutant of the invention are distinguished from those of the prior-art chimeric protein. Therefore, one skilled in the art would not have expected the prior-art protein and the protein of the invention to perform the same function. Accordingly, Ueno does not anticipate the invention.

B. Hirai

The Examiner rejected claims 14, 15, 17, 18, 23 and 24 for alleged anticipation by Hirai *et al.,* Nihon Yakugakkai Dai 121 nenkai Yoshishu, page 7, March 5, 2001, abstract for a meeting of the Pharmaceutical Society of Japan. Applications respectfully traverse the rejection.

Hirai discloses an MDCK cell capable of expressing a chimeric VIP-36 protein, in which the lectin domain is completely replaced by the leguminous lectin domain of BPA or MAH, which is approximately 260 amino acids in size. The difference between the animal lectins and the plant lectins is discussed above.

Because Hirai fails to teach the mutant VIP-36 of the invention, which comprises an alternation of at least one amino acid in the sequence of the native cargo receptor's carbohydrate recognition domain, between amino acid residues 162 and 170, exclusive of the conserved residues at positions 162 and 166, the similar rationale advanced in section III A above applies here.

Applicants submitted a Master's thesis by Takimori accompanying the June 27, 2007 response, evidencing that the chimeric VIP-36 protein of Hirai does not have the function of being capable of transporting glycoproteins selectively in eukaryotic cells. The chimeric VIP-36 protein described in Takimori's Master's thesis and Hirai's chimeric VIP-36 protein share the common feature of replacing the lectin domain with BPA or MAH. Takimori's thesis demonstrates that VIP-36 protein with MHA substitution or BPA substitution has different staining pattern from that of the native VIP-36 protein, indicating loss of glycoprotein transporting capacity of the chimeric proteins.

Because the ERGIC-53 mutant and the VIP-36 mutant of the invention are distinguished from the prior-art proteins in both their functions and their structures, neither Ueno nor Hirai anticipates the invention. Accordingly, withdrawal of the rejection under section 102 is warranted.

IV. Rejection of Claims under 35 U.S.C. §103(a)

The Examiner rejected claims 14, 15, 17, 18, 23, and 24 for alleged obviousness over Itin *et al.*, Molecular Biology of the Cell, 7:483-493, 1996, in view of Yamamoto *et al.*, Journal of Biochemistry, 127:137-142, 2000. Applicants respectfully traverse the rejection.

The Examiner acknowledges that Itin does not explicitly teach the mutant ERGIC-53 comprising an alternation of at least one amino acid in the sequence between amino acid residues 152 and 160 (Action, page 13, lines 6-8). Nevertheless, the Examiner relies on the secondary reference, Yamamoto, for its alleged teaching of carbohydrate binding domains. The rationale behind the rejection is that one skilled in the art would have known which amino acid residues to substitute based on the prior-art knowledge of carbohydrate binding domains and conserved amino acid residues. Applicants submit that the Examiner's rationale can only stand with the aid of impermissible hindsight.

Itin discloses the amino acid alignment of lectins from EcoRL, LOL and ERGIC-53, suggesting that there are at least two domains essential for binding to carbohydrates. *See* the alignment in figure 1, in particular, the underlined regions indicating the conserved motifs, as well as the discussion at page 488, left column, second paragraph.

The Examiner contends that figure 1 of Itin "shows the residues of positions 152 and 156 of ERGIC-53 are highly conservative, as they are shown in the Yamamoto reference." To the contrary, however, the description under Itin's figure 1 explicitly states that the conserved amino acids, D121 (***but NOT D152***) and N156, are marked with a diamond. Therefore, one skilled in the art would not have considered it obvious to align the sequence shown in figure 4 of Yamamoto with the domains identified in figure 1 of Itin to arrive at the mutant of the invention.

Further, figure 4 of Yamamoto shows high homologies among leguminous lectins. One would have expected, therefore, that any amino acid substitution might not alter the carbohydrate binding activity significantly. By contrast, figure 1 of Itin demonstrates lower homology between ERGIC-53 cargo receptor and leguminous lectins. The low level of homology would have militated against attempting to replace the specific domain of a cargo receptor with the corresponding domain of a plant lectin, or randomly to replace the specific domain of a cargo receptor.

Therefore, the combined teachings of Itin and Yamamoto do not fairly suggest the alteration in the specific regions, such as between positions 152-160 for native ERGIC-53 and between positions 162-170 for native VIP-36 as recited in claim 14, the cited references do not render the claimed invention obvious. Accordingly, Applicants respectfully request withdrawal of the rejection.

CONCLUSION

Applicants believe that the present application is in condition for allowance, and an early indication to this effect is requested. Examiner Liu is invited to contact the undersigned directly, should she feel that any issue warrants further consideration.

The Commissioner is hereby authorized to charge any additional fees, which may be required under 37 CFR §§ 1.16-1.17, and to credit any overpayment to Deposit Account No. 19-0741. Should no proper payment accompany this response, then the Commissioner is authorized to charge the unpaid amount to the same deposit account. If any extension is needed for timely acceptance of submitted papers, Applicants hereby petition for such extension under 37 CFR §1.136 and authorize payment of the relevant fee(s) from the deposit account.

Respectfully submitted,

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